REMARKS

Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Claims 32-37 have been amended. Support for the amendments throughout the specification including at page 7 line 18 to page 8, line 27; page 24, lines 9-13; page 33, lines 25-30; and page 42, line 29 through page 43, line 4. No new matter is added by the amendments.

Applicants cancel claims 2-31 and 38-43 without prejudice or disclaimer. These claims were subject to a restriction requirement. Applicants reserve the right to pursue these claims in one or more continuation applications.

37 C.F.R. 1.821(a)(1)/(a)(2)

The Examiner stated that the application fails to comply with 37 C.F.R. 1.821(a)(1)/(a)(2) because pages 85-86 of the specification contain nucleotide sequences that do not have SEQ ID NOs. Applicants have amended the specification to provide SEQ ID NOs for these nucleotides. Applicants also submit with this response a substitute sequence listing containing SEQ ID. NOs. 59 and 60, the amino acid sequence for human prorelaxin H1 and H2, and SEQ ID. NO 61, the amino acid sequence for porcine prorelaxin . Applicants submit the amino acid sequence for human and porcine prorelaxin was well known in the art at the time of filing of the present application (see page 8, lines 7-15 and 21-27).

35 U.S.C. 112, first paragraph

Claims 32-37 were rejected under 35 U.S.C. 112, first paragraph as failing to comply with the Written Description requirement. The Examiner contends that the disclosure does not adequately describe "prorelaxin" as recited in the claims. The Examiner further contends that only rat, porcine, and human species of prorelaxin had been successfully cloned at the time of filing of the instant application.

Although Applicants do not concede the propriety of this rejection, the claims presently are directed to host cells comprising a first nucleic acid encoding a human prorelaxin polypeptide comprising an amino acid sequence of SEQ ID NO: 59 or SEQ ID NO: 60 or mutants thereof having a conservative amino acid substitution at one or more residues, or a porcine prorelaxin or

mutant thereof having a conservative amino acid substitution at one or more residues. Applicants submit this amendment addresses the Examiners rejection and withdrawal of this rejection is therefore requested.

Claims 32-37 were also rejected under 35 U.S.C. 112, first paragraph as allegedly not enabling due to the term "prorelaxin." The Examiner contends that the specification does not adequately characterize prorelaxin by structural or chemical means. Applicants traverse this rejection.

Claims 32-37 as amended recite host cells comprising a first nucleic acid encoding a human prorelaxin polypeptide comprising an amino acid sequence of SEQ ID NO: 59 or SEQ ID NO: 60 or mutants thereof having a conservative amino acid substitution at one or more residues, or porcine prorelaxin or mutant thereof having a conservative amino acid substitution at one or more residues. As described in the specification and acknowledged by the examiner, the amino acid sequences of at least human and porcine prorelaxin were known at the time of filing of the present application. Therefore, Applicants submit that the disclosure provides ample structural characterization of human and porcine prorelaxin. Withdrawal of the rejection is therefore requested.

Claims 32-37 were also rejected under 35 U.S.C. 112, first paragraph as allegedly not enabling transgenic primates. The claims as amended recite that the host cells are isolated host cells. The Examiner has acknowledged that the specification is enabling for isolated animal host cells. Withdrawal of the rejection is therefore requested.

35 U.S.C. 112, first paragraph

Claims 32-37 were rejected under 35 U.S.C. 112, first paragraph as indefinite. The Examiner states it is unclear if Applicants intended to claim isolated host cells. As discussed above, the claims as amended recite that the host cells are isolated host cells. Withdrawal of the rejection is therefore requested.

35 U.S.C. 103(a)

Claims 32 and 34-37 were rejected under 35 U.S.C. 103(a) as unpatentable over Hudson et al. in view of Mulvihill et al. Applicants traverse this rejection.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: (1) the reference must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art to modify the reference; and (3) there must be a reasonable expectation of success. Applicants submit that not all of these requirements have been met because there is no suggestion or motivation to modify the references to disclose all of the claim limitations, and because there would be no reasonable expectation of success.

The present claims recite isolated animal host cells that are not naturally capable of forming secretory granules, and that comprise a first nucleic acid encoding a prorelaxin polypeptide and a second nucleic acid encoding an enzyme that is capable of cleaving the prorelaxin polypeptide to form a mature two chain relaxin polypeptide. Applicants submit that the cited references, alone or in combination, do not teach or suggest host cells having all of these limitations.

Hudson et al. describes the cloning and characterization of a gene sequence coding for human prorelaxin and human relaxin. The Hudson et al. reference describes preparation of the A chain and the B chain by synthetic chemical methods. This reference does not teach or suggest that processing of prorelaxin can or should be conducted in a host cell comprising an enzyme that can cleave the prorelaxin into a mature two chain form. This reference nowhere teaches or suggests host cells that comprise a first nucleic acid encoding a prorelaxin polypeptide and a second nucleic acid encoding an enzyme that is capable of cleaving the prorelaxin polypeptide to form a mature two chain relaxin polypeptide.

Mulvihill et al. does not remedy this deficiency. The Mulvihill et al. reference describes the processing of protein C with or without the KEX2 enzyme. Applicants submit that the Protein C is a different protein than that of prorelaxin and has a single cleavage site with a different sequence. Protein C is secreted via the constitutive pathway. Moreover, Protein C is only cleaved at a single cleavage site and the sequence of the cleavage site differs from that prorelaxin.

In contrast, relaxin is synthesized as a prohormone, which is typically processed through the regulated pathway of secretion. This processing does not occur when the precursor is heterologously expressed in cells containing only the constitutive pathway of protein secretion.

(See the specification at page 7, lines 18 to 26.) Moreover, processing of prorelaxin requires sequential cleavage at two different cleavage sites and the sequence at each of the cleavage sites differs from that of Protein C.

Applicants submit that one of skill in the art would not be motivated to combine or modify Hudson with the disclosure of Mulvihill because the protein in Mulvihill is processed differently than that of prorelaxin. As discussed previously, Protein C is secreted via the constitutive pathway. Processing of proteins through the constitutive pathway is very different than proteins processed through the regulated pathway. There is no teaching or suggestion in Mulvihill that a protein that is normally processed through the regulated pathway would be correctly folded outside of the secretory granules. Moreover, there is not teaching or suggestion that a protein normally processed through the regulated pathway would be compartmentalized with the processing enzyme or that the processing enzyme would be concentrated enough to cleave the protein. In addition, the protein described in Mulvihill has a single cleavage site with a different cleavage sequence than that of prorelaxin. As discussed in Thomas et al, proper processing of proteins that are normally secreted via the regulated pathway may require proper cleavage site structure and accessibility to the cleavage site acting in conjunction with differential expression of a core of processing enzymes. See Thomas at page 5301, end of first paragraph.

There is no teaching or suggestion in Mulvihill that a processing enzyme such as KEX2 could cleave a protein such as prorelaxin that is normally processed through the regulated pathway, has multiple cleavage sites which may not be accessible when produced in a host lacking secretory granules, and that has different sequences at each of the cleavage sites (which may not serve as a substrate for the enzyme).

Moreover, Applicants submit that neither reference teaches a reasonable expectation of success of obtaining a mature two chain form of relaxin in a host cell lacking secretory granules. Hudson et al. does not describe production of prorelaxin or relaxin in any host cell, but rather describes synthesis of each chain using amino acid synthesis and chemical cross linking as described previously. Mulvihill's disclosure is directed to a protein that differs from the claimed protein in secretory pathway, number of cleavage sites and in the sequence of the cleavage sites. Moreover, the processing of prorelaxin is more complicated and includes sequential cleavage

events at two separate cleavage site that each have a different sequence. There is no teaching or suggestion in either reference, alone or combined, of a reasonable expectation of success of achieving a mature two chain form of relaxin.

Based on the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

Claims 32-33 and 35-37 were rejected under 35 U.S.C. 103(a) as unpatentable over Hudson et al. in view of Mulvihill et al. and further in view of Thomas et al. Applicants traverse this rejection.

The present claims recite isolated animal host cells that are not naturally capable of forming secretory granules, and that comprise a first nucleic acid encoding a prorelaxin polypeptide and a second nucleic acid encoding an enzyme that is capable of cleaving the prorelaxin polypeptide to form a mature two chain relaxin polypeptide. Applicants submit that the cited references, alone or in combination, do not provide a motive to combine the references or a reasonable expectation of successes.

The teachings of Hudson et al. and Mulvihill et al. have been discussed above. Applicants submit that these references, alone or in combination, provide no motive to combine the teachings of the reference and provide no reasonable expectation of success. One of skill in the art could not have reasonably expected that the host cells used in the methods of Mulvihill et al. would be capable of coordinating the cleavage and disulfide-bond forming events necessary to produce mature relaxin from prorelaxin, merely because the methods of Mulvihill et al. were successful in producing a completely different protein secreted via a different pathway and with a completely different cleavage site.

Furthermore, Thomas et al do not remedy the deficiencies of Hudson et al. and Mulvihill et al. references. Thomas et al. describes the processing of neuroendocrine hormone propiomelanocortin in BSC-40 cells in the presence or absence of different enzymes. There is no teaching or suggestion in this reference that another hormone produced in a different cell type would be processed similarly. As discussed previously, prorelaxin requires a sequential cleavage at multiple cleavage sites and a disulfide bond that joins the A and B chains. There is no teaching or suggestion that once prorelaxin is produced in a cell without secretory granules, that both of the cleavage sites would be accessible or that the sequence of the each of the cleavage

sites would serve as a substrate for the processing enzyme. As discussed previously, Thomas indicates proper processing includes cleavage site structure and accessibility to the cleavage site acting in conjunction with the processing enzyme. Moreover, the Thomas et al reference shows that the different prohormone convertase enzymes were not able to cleave at every site and completely process the prohormone.

In addition, Applicants also submit even when all the references were combined, they do not provide a reasonable expectation of success of achieving a mature two chain form of relaxin. As discussed previously, Hudson et al. does not describe production of any polypeptides in a host cell. Mulvihill et al. describes production of protein that has a different number and sequence of cleavage sites and is secreted via a different pathway. Thomas et al. is directed to a different protein that is secreted in a different cell type and is processed differently. There is no teaching or suggestion in any of the cited references of the accessibility of the cleavage sites of prorelaxin and/or that each of the cleavage sites of prorelaxin cans serve as substrate for a processing enzyme. Prorelaxin has more complicated processing involving sequential cleavage at two different cleavage sites each of which has a different sequence.

Applicants submit that claims 32 and 34-37 are patentable over the cited references, at least for the foregoing reasons. Withdrawal of the rejection is requested

SUMMARY

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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